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Clinicopathological prognostic factors of oral squamous cell carcinoma: An experience of a tertiary care hospital

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CASE SERIES

Clinicopathological prognostic factors of oral squamous cell carcinoma: An experience of a tertiary care hospital

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Abstract

Locoregional recurrence accounts for majority of the treatment failures in oral cancer patients. Current study aimed to determine the predictors of recurrence and survival in patients with biopsy proven Squamous Cell Carcinoma (SCC) of the oral cavity. This study included 88 patients of squamous cell carcinoma treated at our institution from 2007 till 2013. Primary intervention was surgery in all patients with radiation and chemotherapy in selected patients. Primary end point was locoregional recurrence, distant metastasis and death. Out of 88 patients, 23 (26.1%) patients developed locoregional recurrence and 6 (6.8%) patients developed distant metastasis. Overall survival rate was 77.3%. Follow up ranged from 1 month to 63 months with mean of 17.8±16.2. On multivariate analysis, lymph node involvement and loco-regional recurrence were independent parameters related to decrease overall survival. Lymphovascular invasion, perineural spread, TNM stage and lymph node involvement had significant impact on recurrence.

Keywords: Oral cavity, Squamous cell carcinoma, Recurrence, Metastasis, Radiotherapy.

Introduction

Oral Squamous Cell Carcinoma (OSCC) is the 3rd most common solid tumour in Pakistan, mainly due to addiction. A significant number of recurrent cancers had clear margins and negative neck nodes. This "negative" histologic status and subsequent higher incidence of locoregional recurrence have led many researchers to evaluate the possible predictors of recurrence.[1]

The current study evaluates the impact of various clinicopathological features on survival in Pakistani population.

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Case Series

This was a descriptive cross sectional study. Sample size was calculated by using SAS Sample size calculator on the basis of "Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials". A two-sided log rank test with an overall sample size of 84 subjects was achieved with 80% power at a 0.050 significance level to detect a hazard ratio of 0.5 when the proportion surviving in the group is 0.748.[2] A total of 88 patients with biopsy proven OSCC were selected through non-probability purposive sampling.

Patients who underwent surgical treatment for OSCC with "intent to cure" at Patel Hospital from April 2006 till August 2013 were retrospectively included in this study after obtaining their informed consent. Patients who received palliative treatment and patients who already received initial treatment outside our institution were excluded. The study was approved from institutional ethics committee. Study end points were locoregional recurrence (LR), distant metastasis (DM) and death. Causes of death were classified into: (1) death from LR (2) death from DM (3) death from non-tumour event (4) and death from bronco-pulmonary pneumonia.

Pearson Chi-square test was applied to see the correlation of clinicopathological features with overall recurrence (OR) (LR and DM) and overall survival (OS). Univariate survival curves were plotted using the Kaplan-Meier method, and statistical differences were determined by using the log-rank test. Multivariate analysis was performed using the stepwise backward LR Cox regression hazards model. A p value of <0.05 was considered significant.

Results

A total of 88 patients were included in the study. Male to female ratio was 2.3:1. Patients' age ranged from 22-72 years with mean±SD of 48.26±12. Seventy five (85.2%) cases had history of addiction to different substances including cigarette, pan, betel nut, ghutka (crushed areca nut, tobacco & catechu), naswar (tobacco snuff), etc. Buccal mucosa was the most common site, involving 46 (52%) cases. Tumour size ranged from 0.5 to 6.5 cm

Table-1: Correlation of clinicopathological features of oral squamous cells carcinoma with locoregional recurrence.

Clinicopathological features	Overall Recurrence		p Value
	Yes	No	
Gender			
Male	12 (13.7%)	49 (55.6%)	0.059
Female	11 (12.5%)	16 (18.2%)	
Tumour size			
<2cm	04 (5.4%)	14 (18.9%)	0.927
2-4cm	10 (13.5%)	27 (36.5%)	
>4cm	05 (6.8%)	14 (18.9%)	
Tumour thickness			
<4 mm	05(6.8%)	03(4.1%)	0.035
>4mm	17(23.3%)	48(65.8%)	
Tumour grade			
Well differentiated	04 (4.8%)	17 (20.2%)	0.539
Moderately differentiated	15 (17.9%)	37 (44%)	
Poorly differentiated	04 (4.8%)	07 (8.3%)	
Lymphovascular invasion			
Present	04 (5.6%)	02 (2.8%)	0.028
Absent	16 (22.5%)	49 (69%)	
Perineural Invasion			
Yes	06(7.4%)	04(4.9%)	0.018
No	17(21%)	54(66.7%)	
Surgical margins			
Clear (>5 mm away)	04 (4.5%)	24 (27.3%)	0.052
Close (<5mm away)	18 (20.5%)	32 (36.3%)	
Involved by tumour	01 (1.1%)	09 (10.2%)	
Bone Involvement (n=7)			
Present	02 (28.6%)	03 (42.9%)	0.714
Absent	01 (14.3%)	01 (14.3%)	
Lymph node dissection			
Performed	18 (20.5%)	60 (68.1%)	0.087
Not performed	05 (5.7%)	05 (5.7%)	
Tumour stage			
Stage I	04 (4.6%)	11 (12.6%)	0.029
Stage II	04 (4.6%)	18 (20.7%)	
Stage III	02 (2.3%)	15 (17.2%)	
Stage IVA	13 (14.9%)	20 (23%)	

Table-2: Correlation of clinicopathological features of oral squamous cells carcinoma with overall survival.

Clinicopathological features	Overall Survival		p Value
	Alive	Expired	
Tumour size			
<2cm	14 (18.9%)	04 (5.4%)	0.86
2-4cm	27 (36.5%)	10 (13.5%)	
>4cm	15 (20.3%)	04 (5.4%)	
Tumour thickness			
<4 mm	05 (6.8%)	03 (4.1%)	0.372
>4mm	50 (68.5%)	15 (20.5%)	
Tumour grade			
Well and moderately differentiated	58 (69%)	15 (17.9%)	0.071
Poorly differentiated	06 (7.1%)	05 (6%)	
Lymphovascular invasion			
Present	04 (5.6%)	02 (2.8%)	0.381
Absent	53 (74.6%)	12 (16.9%)	
Surgical margins			
Clear (>5 mm away)	25 (28.4%)	03 (3.4%)	0.083
Close (<5mm away)	34 (38.6%)	16 (18.2%)	
Involved by tumour	09 (10.2%)	01 (1.1%)	
Lymph node involvement			
Present	21 (23.9%)	13 (14.8%)	0.006
Absent	47 (53.4%)	07 (8%)	
Pathologic N stage			
N0	47 (53.4%)	07 (8%)	0.014
N1	11 (12.5%)	04 (4.5%)	
N2a	02 (2.3%)	-	
N2b	07 (8%)	08 (9.1%)	
N2c	01 (1.1%)	01 (1.1%)	
N3	-	-	
Tumour stage			
Stage I	12 (13.8%)	03 (3.4%)	0.056
Stage II	20 (23%)	02 (2.3%)	
Stage III	15 (17.2%)	02 (2.3%)	
Stage IVA	20 (23%)	13 (14.9%)	
Overall recurrence			
Yes	10 (11.4%)	13 (14.8%)	<0.001
No	58 (65.9%)	07 (8%)	

with mean±SD of 3.16±1.39.Tumour thickness ranged from 2 to 60mm with a mean of 14.2±11.68 and median of 11mm. Bone involvement was seen in 5 out of 7 cases which had undergone mandibulectomy. DM was not present in any case at the time of initial diagnosis. Human Papilloma Virus (HPV) infection status could not be checked in these cases since this test is not routinely performed in commercial diagnostic laboratories of our city.

Eleven (12.5%) cases were treated with surgical excision alone, 73 (82.9%) cases received additional radiotherapy and 4 (4.6%) cases had concurrent chemotherapy and radiotherapy. All of the patients received radiation dose of 6600 cGy. The chemotherapy protocol administered in all four patients was 3 cycles of Cisplatin on 3 weekly basis. Reconstruction was done in 52 (59%) cases. Biologic and targeted therapy was not used in any case. Lymph node dissection was performed in 78 cases.

Follow up duration ranged from 1 to 63 months with a mean of 17.8±16.2 and median of 11 months. Twenty three (26.1%) patients developed LR and 6 patients developed DM. Three of these patients developed brain metastasis, 2 developed lung metastasis and 1 developed both brain and lung metastasis. Overall survival rate was 77.3%. Twelve (13.6%) cases died of LR, 6 (6.8%) cases died of DM and single case each with bronchopulmonary

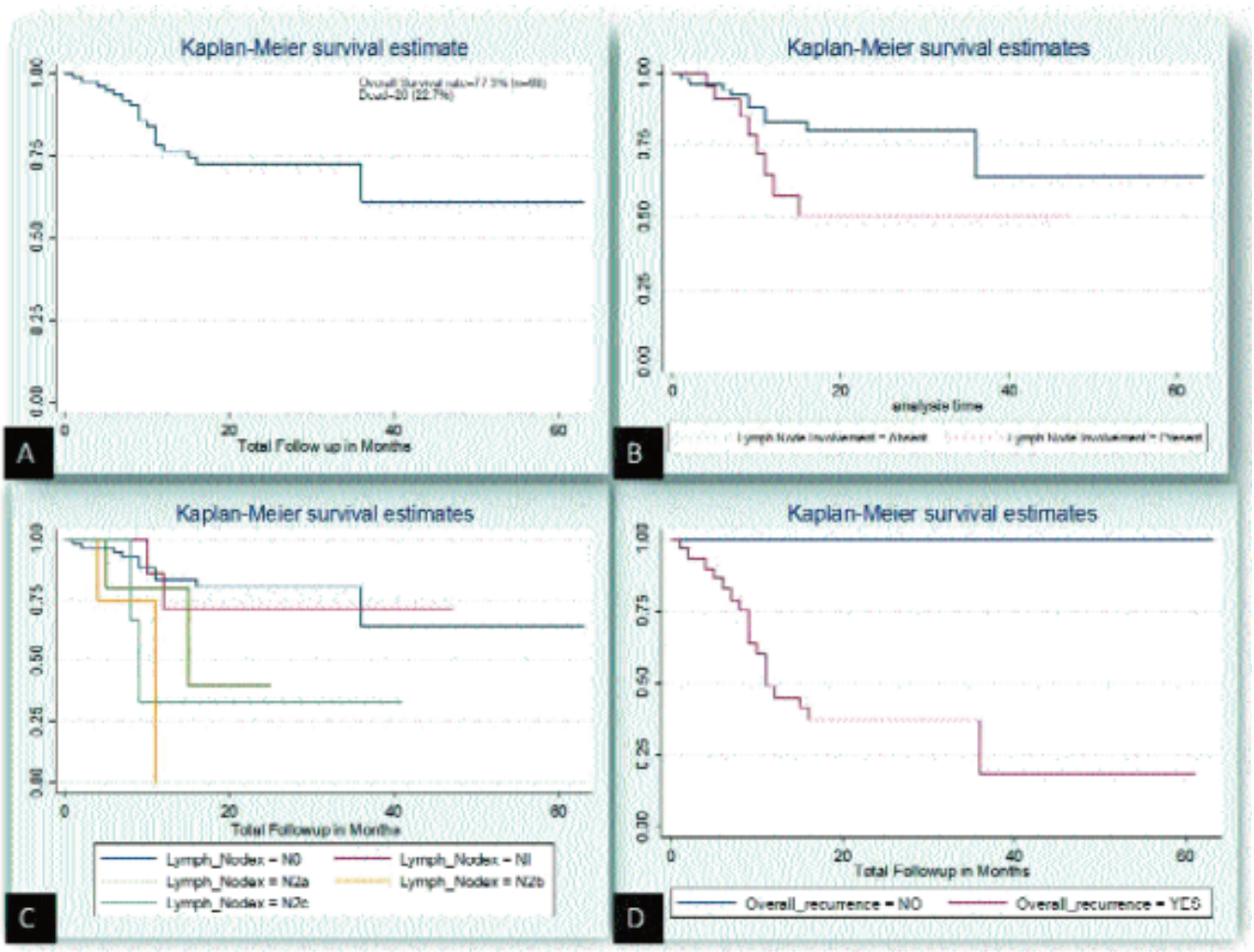

Figure-1: (A) Kaplan-Meier curve for overall survival. Kaplan-Meier curves showing significant reduction is overall survival with (B) Lymph node involvement (C) Nodal stage and (D) Recurrence.

pneumonia and non-tumour related cause.

In univariate analysis, ≤4mm tumour thickness, lymphovascular invasion (LVI), perineural invasion (PNI) and TNM stage were significantly associated with increased LR (Table-1). In multivariate analysis, LVI was the only independent parameter related to LR (p = 0.004).

In univariate analysis, lymph node involvement, higher nodal stage and OR were significantly associated with decreased overall survival (Table-2). In multivariate analysis, lymph node involvement and LR were the independent parameters related to decreased OS (p= 0.004 and p= 0.001, respectively).

Discussion

OS of OSCC ranges from 54.6% -74.8% in reported literature.[2] OS in our series was 77.3% and recurrence free survival was 73.9%.

OSCC is more commonly encountered in males with M:F of 1.5:1.[3] In our study, M:F was 2.3:1. Studies have reported higher incidence in patients above 45 years.[4] In our experience, the LR rate and death rate were almost similar in the two age groups.

High incidence of OSCC in the subcontinent is attributed to the addiction of cigarette and tobacco.[5] We evaluated the risk of developing recurrence with the addiction but no correlation was observed. The commonest site of tumour involvement in the subcontinent population is buccal mucosa due to tobacco chewing.[5] Buccal mucosa, tongue and lower alveolar ridge were the most common tumour sites in our series. The highest rate of recurrence

was seen in the tumours of lower alveolar ridge.

Several studies have demonstrated that tumour size is related with lymph node involvement, recurrence and overall survival.[6] In our study, tumour recurrence rate and death rate was similar in different categories of tumour size. Tumour thickness is a better predictor of disease progression.[7] In contrast, we observed significantly higher recurrence rate in patients with less tumour thickness.

Histologic grade has proved to be a good predictor of prognosis in few studies while other studies failed to demonstrate it.[8] Although, poorly differentiated tumours in our study showed the highest rate of recurrence and death but statistical significance was not achieved.

LVI is a well-known risk factor for LR and DM.[7] After multivariate analysis, LVI proved to be the only independent factor predictive of recurrence in this study (p=0.004).

PNI is also related to tumour recurrence.[9] In our cohort of patients, PNI was significantly associated with a higher recurrence rate (p=0.018) but it was not an independent prognostic factor after multivariate analysis.

Tumour recurrence was observed in 2 out of 5 (40%) patients of our study who had bone involvement. All these patients, received additional radiotherapy which was successful in achieving good disease control. Surgical resection with closed margins was associated with the highest recurrence rate (p=0.052) and death rate (p=0.083) in our study. Interestingly, resections with positive margins did not show poor outcome and probably the adjuvant radiotherapy was successful in controlling the tumour spread.

Cervical lymph node involvement is one of the most important poor prognostic factors[6] Lymph node involvement and higher 'N' stage were significantly associated with poor survival (p=0.006 and p=0.014 respectively), but no significant association was seen with tumour recurrence. The highest death rate was seen in N2b stage category. After multivariate analysis, lymph node involvement proved to be the sole independent factor predicting poor survival (p=0.004).

Tumour stage has well-established relation with the survival in OSCC.[9] We did not observe significant difference in outcome among T stage categories. However, when N stage was also combined with T stage and an overall tumour stage was assessed, a significantly higher recurrence rate was observed with higher tumour stage (p=0.029), the maximum being seen in stage IV. Moreover, higher tumour stage was also associated with poor survival (p=0.056), the worst observed again in stage IV.

The combination of reconstructive surgery and radiotherapy has resulted in improved overall survival.[10] We did not observe any difference in recurrence and survival related to the treatment modalities used. Majority of the patients were treated with surgery along with radiotherapy which provided good disease control. Twenty (27.3%) out of these 73 patients developed LR and 17 (23.2%) died of the disease.

LR and DM have adverse impact on survival.[2] Similarly, we observed significantly worse survival in these patients (p<0.001). Thirteen (56.5%) out of 23 patients with LR and all 6 patients with DM died of the disease.

Patient survival was adversely affected in the 20 -30 months' time span following treatment completion. After 36 months, survival pattern remained stable (Figure-1A).

When the parameters adversely related to the survival were analyzed by using Log rank test, the mean survival duration of patients with lymph node involvement was significantly lower than the mean survival duration of patients without lymph node involvement (32.7 versus 50.6 months). Median survival duration was 15 months with confidence interval of 8.05-21.9 and significant p value of 0.002 (Figure-1B).

The mean survival duration of patients with nodal stage N2c was significantly lower than the mean survival duration of patients with nodal stage N0 (9 versus 50.6 months). Median survival duration was 9 months with confidence interval of 9.0-9.0 and highly significant p value of <0.001(Figure-1C).

The mean survival duration of patients with recurrence was significantly lower than the mean survival duration of patients who were disease-free (26.3 versus 54.5 months). Median survival duration was 11 months with confidence interval of 9.53-12.5 and highly significant p value of <0.001 (Figure-1D).

Since this study was retrospectively conducted in a single tertiary care center, it has few limitations including small sample size, variable follow up duration and treatments given to the patients. Therefore, prospective multi-institutional studies on larger cohorts are needed to validate the findings of these studies.

Conclusion

LVI, PNI, TNM stage and nodal involvement were

identified to correlate with the poor outcome. Higher recurrence rate in tumours with a thickness of <4mm and clear margins point out towards the success of adjuvant radiotherapy in controlling locally advanced disease and considering this treatment option in early tumours also.

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References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v.1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11.Lyoun, France: International Agency for Research on Cancer; 2013. [Online] [Cited 2017 Feb 26]. Available from: URL: http://globocan.iarc.fr
2. Jerjes W, Upile T, Petrie A, Riskalla A, Hamdoon Z, Vourvachis M, et al. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients.Head Neck Oncol. 2010;2:9.
3. Bagan JV, Scully C. Recent advances in Oral Oncology 2007: epidemiology, aetiopathogenesis, diagnosis and prognostication.Oral Oncol. 2008;44:103-8.
4. Warnakulasuriya S, Mak V, Möller H. Oral cancer survival in young people in South East England. Oral Oncol. 2007;43:982-6.
5. Naz S, Salah K, Khurshid A, Hashmi A, Faridi N. Head and neck squamous cell carcinoma-comparative evaluation of pathological parameters in young and old patients. Asian Pac J Cancer Prev. 2015;16:4061-3.
6. Woolgar J, Rogers S, Lowe D, Brown J, Vaughan ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. Oral Oncol. 2003;39:130-7.
7. Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol. 2006;42:229-39.
8. Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, et al. Prognostic factors of clinically stage I and II oral tongue carcinoma-A comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, martinez-gimeno score, and pathologic features. Head Neck. 2002;24:513-20.
9. Sobin, LH, Compton CC. TNM seventh edition: What's new, what's changed. Cancer 2010;116:5336-9.
10. Vaughan ED. Functional outcomes of free tissue transfer in head and neck cancer reconstruction. Oral Oncol. 2009;45:421-30.